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A Database survey of equine tumours in the United Kingdom

Summary

Reasons for performing study: Survey data on equine tumours are sparse compared with other species and may have changed over time.

Objectives: To describe the most frequently diagnosed equine tumours recorded by a diagnostic pathology laboratory over 29 years, to identify signalment factors associated with tumour type, and to identify any changes in the tumours diagnosed or the signalment of cases during the study period.

Study design: Observational; survey data are presented with case: case comparisons.

Methods: The records of all neoplastic equine histology submissions to the University of Bristol (January 1982 - December 2010) were accessed from a database, and a list of diagnoses compiled. The six most commonly diagnosed tumour types were analysed using logistic regression to identify signalment factors associated with tumour type. The overall population of equine tumour submissions and the relative frequency of diagnosis of the most common tumour types were compared between decades.

Results: 964 cases were included. The most frequently diagnosed tumours were: sarcoid (24% cases), squamous cell carcinoma (SCC) (19%), lymphoma (14%), melanoma (6%), gonadal stromal tumour (6%) and mast cell tumour (MCT) (4%). With sarcoid, Thoroughbred/Thoroughbred X and gelding as reference categories: increasing age was significantly associated with the odds of each of the other tumour types, mares were at

reduced risk of SCC, Arab/ArabX had a higher risk of MCT, Cob/CobX had an increased risk of SCC and MCT, and Ponies had an increased risk of melanoma. The mean age of submissions increased in each successive decade and the breed composition became broader. Sarcoids and lymphoma formed a smaller proportion of diagnoses in later decades.

Conclusions and Potential Relevance: The types of tumours submitted to this laboratory have changed over the last three decades. Current data informs clinicians and researchers; further studies are warranted to follow trends.

Introduction

Surveys of tumour types and incidence in animals are few compared to those in people [1]. In horses, several surveys between 1975 and 1983 compared the relative frequencies of tumour types involving a range of body systems[2-5], although one [3], concentrated on those involving the skin. More recently, Valentine [6] and Shaffer *et al* [7] reported similar data for cutaneous neoplasia. In many countries, including the UK, there is an increasing number of geriatric horses, over 15 years old [8]. In the horse, the risk of malignant tumours is more strongly age dependent than the risk of benign tumours [9]. Changes to the mean age of horses in the population may therefore be associated with changes in the incidence of different tumour types. Thus, more current data on the most frequently diagnosed equine tumour types should inform veterinary surgeons treating clinical cases, provide data for comparative research and identify research priorities. Furthermore, breed and sex predilections for many tumours are poorly described in equine populations [2-5; 10] and there has been no attempt to identify whether the most commonly diagnosed tumour types have changed over time. The aims of this study were: to describe the most frequently diagnosed equine tumours from samples submitted to a diagnostic pathology laboratory over an extended time period, to identify any signalment factors associated with specific tumour types, and to identify any changes in the signalment of cases submitted and tumours diagnosed by the laboratory over time.

Materials and Methods

The diagnoses, without review, of all equine histology submissions to the Department of Veterinary Pathology, University of Bristol, including biopsy and post mortem samples, from the University of Bristol's equine centre, and from referring veterinary surgeons from January 1982 to December 2010, were accessed from the Department of Veterinary Pathology database. The records of cases with a histological diagnosis of neoplasia (including sarcoid) were retrieved. The study aimed to include only cases for which a diagnosis was requested and where the neoplasia was considered to be clinically significant, thus cases in which a tumour was detected incidentally, such as benign pituitary adenomas or mesenteric lipomas identified as coincidental findings on *post mortem* examination were excluded.

Cases were grouped into categories according to the original histological diagnosis. Some diagnoses were considered synonymous and were grouped together, for example gonadal stromal tumours included ovarian granulosa cell tumour, sex cord-stromal tumour and ovarian thecoma. Some rare tumour types or poorly differentiated tumours were grouped into related categories such as 'other carcinomas'. Cases in which more than one significant tumour type was diagnosed in the same horse were excluded from analysis. Information on patient signalment (i.e. age, breed and gender) was retrieved from details provided at the time of submission.

Initially, each tumour type was listed in order of frequency (total number of cases diagnosed during the study period). Statistical analysis was performed on the six most commonly diagnosed tumour types with all other tumour types included as a separate, "Other Tumours"

group. For statistical analysis: age was recorded in complete years; breeds/types were classified into groups as follows: 1) Thoroughbred (TB) and “Thoroughbred cross/Sport horse” including Irish Sport Horse, Irish Draught x TB, Hunter and Eventer 2) “Cob” including Cob cross 3) “Arab” including Arab cross 4) “Pony” (including specified pony breeds and unspecified pony types) 5) “Other breeds” comprising all other breed types and donkeys. Gender was classified as gelding, mare or stallion.

To identify associations between the dependent variable, tumour type, and signalment variables (age, breed and gender) univariable analysis was performed using a one way ANOVA for age (after testing the distribution of age for normality) and Chi Squared tests for independence for breed and gender. When significant associations were identified a case-case design was used with binary logistic regression to assess the impact of the three signalment variables (age, breed and gender) on the odds of a diagnosis of a specific tumour type using sarcoid, Thoroughbred/Thoroughbred cross and gelding as reference categories.

To investigate any changes in submissions to the laboratory over time, the data were compared by decade of submission. Cases were divided into three groups by date of submission as follows: January 1982-December 1990 (80's), January 1991 to December 2000 (90's) and January 2001 to December 2010 (00's). The signalment data for all submissions were compared between decades. Subsequently, the proportion of diagnoses of each of the six main tumour types and the “other tumours” group were compared between decades. Mean age in each decade was compared using a one-way ANOVA with Tukey's test for *post hoc* comparisons.

Associations between decade of submission and gender, breed and tumour type were assessed using Chi Squared tests with *post hoc* tests using a Bonferroni correction.

Finally, the variable, 'decade of submission' was added to the logistic regression models relating signalment to tumour type to identify whether associations between tumour type and decade of submission were due to changes in patient signalment or associated with other factors.

Submissions from the 00's were the reference category. All data were analysed using statistical software (IBM SPSS 22). Differences were considered significant if $p < 0.05$.

Results

In total 964 cases were included. Age was recorded in 858 cases and its distribution was approximately Normal. Overall, the mean age was 12.2 years (range 0- 40 years). Gender was recorded in 916 cases. There were 524 geldings, 334 mares or fillies, and 58 entire males. Breed information was available in 880 cases. There were 337 Thoroughbred and Thoroughbred cross/ Sports horses, 242 Ponies, 111 Cob or Cob crosses, 59 Arabs or Arab crosses, and 131 other breed types including 18 Donkeys. The most frequently diagnosed tumour types, their proportion of total tumour diagnoses, and a summary of age and gender data are shown in Table 1.

Association between signalment and tumour type

The six most commonly diagnosed tumour types and percentage of diagnoses were: sarcoid (24%), squamous cell carcinoma (SCC) (19%), lymphoma (14%), melanoma (6%), gonadal

stromal tumour (GST) (6%) and mast cell tumour (MCT) (4%). Statistical analysis was performed on these tumour types. Age ($p=0.001$), breed ($p<0.001$) and gender ($p<0.001$) were all associated with tumour type. Table 2 shows the significant signalment variables associated with the odds of a diagnosis of each tumour type revealed by binary logistic regression with sarcoid, TB/TBX and gelding as reference categories.

When compared with sarcoids, age increased the odds of diagnosis for the five other main tumour types. The effect was most pronounced for SCC with an odds ratio (OR) of 1.3 for each increasing year of age. Breed effects were found for SCC, melanoma and MCT, and were most pronounced for Arab/ArabX and MCT (OR = 15). Ponies were associated with an increased risk of melanoma (OR=2.9). Cob/CobX was associated with an increased risk of MCT (OR = 4.9) and SCC (OR = 2.7). A gender association was identified for SCC; mares were at a reduced risk (OR =0.36). Gender was not included in the model for GST, as these tumours only occur in mares; the stallion category was excluded from the MCT model as no MCTs occurred in stallions.

Chi Squared model evaluation revealed all models to be statistically significant. Cox and Snell and Nagelkerke pseudo R squared values revealed that the model for SCC provided the best fit (with values of 0.39 and 0.53 respectively) whilst the model for GST provided a very poor fit (0.047 and 0.075 respectively).

Comparison between decades

Of the 965 cases, 221 were submitted during the (80's), 297 cases during the (90's) and 446 cases during the (00's).

The mean ages of all submissions were 10.3 years, 11.8 years and 13.3 years for the 80's, 90's and 00's respectively. The mean age for the 00's was higher ($p<0.01$) than either the 80's or 90's. The mean age in the 90's was higher than for the 80's ($p=0.026$).

The percentage of submissions from each breed type within each decade of the study are shown in figure 1; statistically significant ($p<0.05$) differences between decades are labelled on the histogram. The percentage of submissions from TB/TBX horses decreased in each decade and was lower ($p<0.05$) during the 00's (30% submissions) than the 80's (49% submissions). The percentage of submissions from Cob/CobX's was higher during the 00's (16%) than in the 90's (9.2%). The percentage of submissions from the Other Breeds group increased in each successive decade comprising 22%, 12% and 5% of submissions in the 00's, 90's and 80's respectively. No significant differences were observed in the relative proportions of submissions from each gender in each decade.

The percentage of diagnoses for each of the main tumour types was compared between decades (figure 2). The percentage of submissions diagnosed as sarcoid was lower ($p<0.05$) in the 00's (20%) than in the 80's (31% of submissions). The percentage of submissions diagnosed with lymphoma was also lower ($p<0.05$) in the 00's (8%) than in the 90's and 80's (16% and 22%). The percentage of other tumours (i.e. those not in the six main groups) was higher ($p<0.05$) in the 00's (35%) than in the 90's and 80's (26% and 18%). There were no significant differences in the proportions of SCC, melanoma, GST or MCT between decades.

Finally, the variable "decade of submission" was added to the regression models relating signalment to tumour type (adding the 00's as a reference category) to identify whether

differences between decades in the frequency of the main tumour types were the result of changes in signalment of submitted cases or were associated with other factors.

The decade of submission had a significant effect on the odds of a diagnosis of lymphoma.

Lymphoma was diagnosed more frequently in the 80's (OR =2.4, CI 1.3-5.4, p= 0.008) and the 90's (OR= 2.3, CI 1.1-4.5, p=0.022) compared with the 00's. The addition of the variable decade of submission also altered the model for lymphoma to reveal increased odds of a diagnosis of lymphoma in stallions (OR 4, CI 1.1-14). There was no significant association between decade of submission and the odds of diagnosis for SCC, melanoma, MCT or GST. The addition of the variable decade of submission did not significantly alter the previous models for SCC, melanoma and MCT but for GST the addition of the variable decade to the model reduced the quality of the model such that Chi squared tests of model fit were no longer statistically significant

Discussion

The present study describes the most frequently diagnosed tumour types in horses from samples submitted to a UK-based diagnostic laboratory over a 29 year period, with signalment data for the most common tumour types. Associations between signalment and some tumour types were shown. The signalment of the population submitted to the laboratory changed between decades, as did the relative frequency of diagnosis of several tumour types.

Limited comparisons can be made between the most frequently diagnosed tumours in the present study and other studies with a similar design [2-4] (table 3). In the present study, and those of Bastianello [4] and Sundberg *et al* [2], sarcoids were the most frequently diagnosed equine tumour. The histological definition of equine sarcoid may vary and some tumours

classified as fibromas by Baker and Leyland [3] may have been classified as sarcoids by other groups. In the present study, the proportion of sarcoids or benign fibromatous skin tumours was lower than in other studies, in contrast, lymphoma was diagnosed more frequently. The present study was less dominated by a small number of common tumour types, for example the two most commonly diagnosed tumours (sarcoïd and squamous cell carcinoma) comprised over 50% of submissions (51%, 68%, and 62%) in the other studies [2-4], but only 43% in this study. The greater representation of less common tumour types in the present study is most prominent in the 00's (figure 2). When data from the 00's were analysed alone, the 3 most commonly diagnosed tumour types (sarcoïd, squamous cell carcinoma and lymphoma) accounted for only 47% of submissions, compared with 64%[3], 74%[2], and 70%[4] in the previous studies.

The relatively low proportion of sarcoids in the present study may be related to clinician behaviour or other population differences. The prevalence of sarcoids may have been under-represented if clinicians were reluctant to biopsy sarcoids due to the reported risks [11; 12] or if some clinicians were more confident to reach a diagnosis of sarcoïd without histological confirmation. Signalment differences between study populations may be relevant. The mean age of all submissions in the present study was 12.2 years and increased in each decade. The mean age of sarcoïd submissions (8 years) was younger than for the other main tumour types. The mean age of subjects (7.4 years) was only available for one other study[2]. Complete breed analysis was not available in other studies but from the available data it appears that the present study included a higher proportion of ponies and a lower proportion of quarter horses. Quarter horses are at increased risk of sarcoids [13; 14]. The cause of the higher proportion of

lymphoma cases in the present study and in particular in the 80's and 90's is unknown. The increased odds of a diagnosis of lymphoma in the 80's and 90's was independent of the signalment variables considered, although age was also an independent risk factor for a diagnosis of lymphoma compared with sarcoid. No risk factors for lymphoma have been described in horses [15] in contrast to people in which numerous risk factors have been identified [16].

In the present study, several signalment factors were associated with tumour type. When compared with sarcoids, age was associated with increased odds of diagnosis for all of the five other main tumour types and the effect was most pronounced for SCC (OR= 1.3 for each year). This is consistent with a previous report that the risk of malignant tumours is more age dependent than benign tumours in horses [9].

Breed effects (when compared with TB/TBX) were identified for MCT, SCC and melanoma. The strongest association was for MCT and Arab/ArabX (OR = 15, $p < 0.001$). An association between Arabians and MCT has been suggested previously, but not statistically demonstrated [17].

Associations between MCT and SCC with Cob/CobX's were also demonstrated and have not, to the authors' knowledge, been reported previously. Previous studies have remarked on the high prevalence of penile SCCs in ponies but have suggested that this may primarily relate to an older pony population [18; 19]. This assertion is supported by the present study in which ponies were not at increased risk of SCC when age was controlled for. In contrast, ponies had a higher odds of a diagnosis of melanoma. Melanoma is strongly associated with coat colour [20]

and high numbers of grey ponies may have influenced the association with pony breeds in the present study.

Associations between gender and tumour type were identified for SCC and (after the inclusion of decade as a variable) lymphoma (gender was excluded from the model for GST). The lower odds of a diagnosis of SCC in mares, when compared to geldings, is likely to be related to the proportion of SCC located in the penile and preputial areas. The association between lymphoma and stallions is not easily explained but may be a spurious finding related to the low numbers of stallions included.

The signalment of cases submitted to the laboratory changed in each decade. The mean age of submissions increased in each successive decade. Other studies have reported a trend to keep horses into older age and to provide higher levels of veterinary care to older horses [8; 21]. The results of the present study reflect this observation. The change in breed composition of submissions (as the proportion of submissions from Thoroughbreds decreased and the proportion of submissions in the “other breeds” group increased) in each successive decade is difficult to interpret but could also represent changes in the wider equine population.

The number of tumour samples received by the laboratory increased in each decade (although only 9 years were included in the “80’s”). These data may reflect submission preferences of veterinary surgeons or increasing owner and veterinary interest in the diagnosis and treatment of equine tumours [22].

The relative incidence of different tumour types diagnosed at this laboratory also changed over different decades. The relative proportions of sarcoids and lymphoma decreased whilst the

proportion of “other tumours” (i.e. those other than the six most commonly diagnosed tumours) increased. The increased variety in the types of tumour diagnosed in successive decades may reflect signalment factors such as the increasing proportion of submissions in the “other breeds” category, and the increasing age of subjects. Unfortunately there is insufficient published data from other laboratories to provide a context in which to interpret these trends, and explanations therefore remain speculative.

The present study suffers significant limitations. Only the relative frequency of diagnosis of different tumour types could be compared, rather than the true frequency as the size of the denominator population is unknown. Numerous selection biases affect the samples that were submitted and a suitable control population was not available. Selection bias may have been a particular limitation because many equine tumours never present for veterinary examination for reasons including: clinician preference, cost, inaccessibility, and clinical (rather than histological) diagnosis. The application of inferential statistical tests to these data assumes that the samples submitted are representative of a larger population. This assumption may be incorrect and study findings must be interpreted with caution. Other limitations include the accuracy of the data that was provided on the original submission forms that could not be verified and in some cases was incomplete. Diagnoses also were made by a number of different pathologists and may be subject to variation between individuals.

Conclusion.

These data inform differential diagnosis lists for veterinary surgeons and pathologists, allow comparisons with other studies and reveal trends to direct future research.

In common with previous studies, sarcoids were the most frequently diagnosed equine tumour type, but lymphoma was diagnosed more frequently than in other studies. Associations between signalment and tumour type were identified. Over the study period sarcoids and lymphoma have formed a smaller proportion of tumour diagnoses such that the relative incidence of less common tumours has risen. The reasons for these changes are unclear but in part may be related to an ageing population.

Table and Figure legends:

Table 1: Tumour types, frequency of diagnosis, age and gender data.

Table 2: Summary data of signalment factors associated with the dependent variable tumour type using binary logistic regression with sarcoid, TB/TBX and gelding as reference categories. Factors that were significant ($p < 0.05$) are shown in bold (other categories of the same variable are also listed).

Table 3: Results of the present study compared with other studies with a similar design.

Figure 1: The percentage of equine tumour submissions from each group for each decade of the study period. Each letter denotes values that are significantly different ($p < 0.05$)

Figure 2: The percentage of equine tumour submissions from each of the main tumour types for each decade of the study period. Upper case letters denote groups that differ significantly from the group denoted by the same letter in lower case. ($p < 0.05$).

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